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Jeniffer Dantas Ferreira[1], Arnaldo Cézar Couto[1], Maria do Socorro Pombo-de-Oliveira[2], Sergio Koifman[1], and the Brazilian Collaborative Study Group of Infant Acute Leukemia[3].

[1] Environment and Public Health Post-graduation Program, National School of Public Health, Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, Brazil

[2] Pediatric Hematology-Oncology Program, Research Center, Instituto Nacional de Câncer/Rio de Janeiro, Rio de Janeiro, Brazil

Correspondence to:
Sergio Koifman
Environment and Public Health Post-graduation Program, National School of Public Health, Oswaldo Cruz Foundation (FIOCRUZ)
Rua Leopoldo Bulhões 1480, Rio de Janeiro, RJ, 21041-210, Brazil
Telephone number: +55 21 2598-2634
e-mail: *koifman@ensp.fiocruz.br*;

Brazilian Collaborative Study Group of Infant Acute Leukemia Collaborators
Jozina Maria de Andrade Agareno[1], Flávia Nogueira Serafim Araújo[1], Núbia Mendonça[1], Cynthia Curvello Neves[1], Alejandro Aranciba[2], Renato Melarangno[2], Rosania Baseggio[3], Atalla Mnayarji[3], Reinaldo Del Belo[4], Jane Dobbin[4], Silvia Brandalise[5], Vitória Pinheiro[5], Lilian M Burlacchini de Carvalho[6], Eni Guimarães de Carvalho[6], Tereza Cristina Cardoso[6], Imaruí Costa[7], Jose Carlos Cordoba[8], Isis Q Magalhães[8], Virginia M Coser[9], Maria Lucia Lee [10], Flávia Pimenta[11], Mara A.D.Pianovsky[12], Terezinha JM Salles[13], Fernando Werneck [14] and César Bariani [15]

[1] Pediatric Hematology-Oncology Service, Hospital Santa Izabel, Salvador, Bahia, Brazil

[2] Pediatric Hematology-Oncology Service, Hospital Santa Marcelina, Sao Paulo, São Paulo, Brazil

[3] Pediatric Hematology-Oncology Service, Hospital Rosa Pedrossian, Campo Grande, Mato Grosso do Sul, Brazil

[4] Research Center and Hematology Service, Instituto Nacional de Câncer, Rio de Janeiro, Rio de Janeiro, Brazil

[5] Centro Infantil de Investigações Hematológicas D. Boldrini, Campinas, São Paulo, Brazil

[6] Pediatric Hematology-Oncology Service, Hospital Martagão Gesteira, Salvador, Bahia, Brazil

[7]Pediatric Hematology-Oncology Service, Hospital Joana de Gusmão, Florianópolis, Santa Catarina, Brazil

[8] Hospital de Apoio Brasília, Unidade de Onco-Hematologia Pediátrica, Brasília, Distrito Federal, Brazil

[9]Departamento de Hematologia, Universidade de Santa Maria, Santa Maria, Rio Grande do Sul, Brazil

[10] Pediatric Oncology Institute- GRAAC, São Paulo, São Paulo, Brazil

[11] Hospital Napoleão Laureano, João Pessoa, Paraíba, Brazil

[12] Hospital Pegueno Principe, Curitiba, Paraná, Brazil

[13] Hospital Oswaldo Cruz, CEON, Recife, Pernambuco, Brazil

[14] Pediatric Oncology Section, Hospital dos Servidores do Estado do Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brazil

[15] Serviço de Transplantes de Medula do Hospital Araújo Jorge, Goiania, Goiás, Brazil

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ABSTRACT

Background: An association between pesticides exposure and cancer has been suggested. Infant leukemia is a rare neoplasm and its association with maternal pesticide exposure has been poorly explored.

Objectives: To investigate the association between pesticide exposure during pregnancy and leukemia in children < 2 years of age.

Methods: A hospital-based case-control study was carried out in 15 Brazilian hospitals in 1999-2007. Mothers of 252 cases and those of 423 controls were interviewed. Information on pesticide exposures 3 months before pregnancy, throughout pregnancy, and during breastfeeding was obtained. Unconditional logistic regression was used to estimate adjusted odds ratios (adj. ORs) for associations between pesticide exposures and leukemia.

Results: Associations with ever use of pesticides during pregnancy were observed for acute lymphoblastic leukemia, ALL (adj. OR 2.10; 95% CI: 1.14, 3.86) and acute myeloid leukemia, AML (adj. OR 5.01; 95% CI: 1.97, 12.7) in children age 0–11 months, and with ALL (adj. OR 1.88; 95% CI: 1.05, 5.23) at age 12-23 months. According to reported maternal exposure to permethrin, higher risk estimates were verified for children 0-11 months, adj. OR 2.47; 95% CI: 1.17, 5.25 for ALL, and adj. OR 7.28; 95% CI: 2.60, 20.38 for AML. Maternal pesticide exposure related to agricultural activities showed an adj. OR 5.25; 95% CI: 1.83, 15.08 for ALL, and an adj. OR 7.56; 95% CI: 1.83, 31.23 for AML.

Conclusions: These results support the hypothesis that pesticide exposure during pregnancy may be involved in the etiology of acute leukemia in children younger than age 2 years.

INTRODUCTION

Pesticide exposure is a public health concern worldwide. In Brazil, a study conducted in two stages among small-scale fruit farmers revealed that 19% of them had reported at least one poisoning episode (4% in the year previous to interview). Even at this stage, it was concluded that 11% of all episodes were probable cases of acute poisoning according to WHO criteria (Faria et al. 2009). Moreover, pesticide use also has been associated with chronic diseases such as cancer, including childhood leukemia, 0-14 yr. (Bassil et al. 2007; Infante-Rivard and Weichenthal 2007; Turner et al. 2010; Zahm and Ward 1998).

Infant leukemias are rare acute leukemias diagnosed within the first 12 months of age, although some researchers include cases up to 18 months of age (Alexander et al. 2001; Pombo-de-Oliveira and Koifman 2006). DNA alterations during the periconceptional period or pregnancy, which may be caused by chemical substances and other environmental exposures, are potential risk factors for infant leukemias (Buffler et al. 2005; Lafiura et al. 2007). Previous studies have reported associations between childhood leukemia and maternal exposure to pesticides (Ma et al. 2002; Meinert et al. 2000; Menegaux et al. 2006; Rudant et al. 2007; Monge et al. 2007).

However, very few studies of pesticides and leukemia in very young children have been published. Additionally, most studies of association between childhood leukemias and pesticides focused on parents' occupational exposures (Colt and Blair 1998; Monge et al. 2005; Perez-Saldivar et al. 2008; Rudant et al. 2007; Wigle et al. 2009), and a few considered the use of household pesticides during the prenatal period (Lafiura et al. 2007; Meinert et al. 2000; Monge et al. 2007; Zahm and Ward 1998).

A case-control study of risk factors for leukemia in children under 2 years was conducted in Brazil, and an adj. OR 2.18 (95% CI: 1.53, 2.13) was reported in association with maternal exposure to pesticides (Pombo-de-Oliveira and Koifman 2006). The present

investigation aimed to extend such previous exploring analysis on maternal pesticides exposure and leukemia in the offspring.

METHODS

Study Population

This investigation is part of a multicenter study called "Multi-institutional Study of Infant Leukemia: Contribution of Immunomolecular Markers in Distinguishing Different Etiopathogenic Factors", which focuses on the investigation of biomarkers of leukemia diagnosed in children younger than 2 years in Brazil. Participants (n=675) were recruited from 15 selected hospitals in all geographic areas in the country but the Amazon, including cities in the Southern Region, the Southeast, the Northeast, and the Middle West.

Study Design

This is a hospital-based multicenter case-control study in which controls were frequency matched with leukemia cases according to age (0 – 23 months) and enrolled from the same geographic areas where cases were diagnosed.

Data were obtained by in person interviews carried out between 1999-2007 with mothers of newly diagnosed patients recruited from the Brazilian National Health System centers providing oncologic care for pediatric patients and from general hospitals.

Cases (n=252) were defined as children < 24 months of age with a conclusive diagnosis of acute lymphoid leukemia, ALL (n= 193), or acute myeloid leukemia, AML (n=59) confirmed by morphology, immunophenotype and standard cytogenetic-molecular methods.

Controls (n=423) were selected from children < 24 months of age with non-malignant diseases that were patients at the Brazilian National Health System oncologic centers where

cases were recruited, or patients of general hospitals in the same cities . These hospitals from which controls were recruited had the same catchment areas of those of cases. Controls included children with infectious and parasitic diseases (n=124, 29.4%); non-malignant hematological diseases (n=83, 19.6%); asthma and bronchitis (n=43, 10.2%); hemangioma (n=40, 9.4%); severe diarrhea (n=39, 9.2%); cardiovascular diseases (n= 25, 5.8%); and other non-malignant conditions (n=69, 16.4%).

Children with congenital syndromes, myelodisplasia, adoptive parents, or unknown biological mothers, were not eligible to be enrolled, and controls with a cancer diagnosis were excluded. Participation of invited cases and controls in the study was, respectively, 96 and 95% (Pombo-de-Oliveira and Koifman 2006).

Data Collection

The study was specifically designed to collect information on several environmental exposures potentially associated with leukemogenesis. Data were collected by in-person interviews with case and control mothers at the hospital. A standardized questionnaire was used for all participants, including information on the environmental exposures during pregnancy, including use of pesticides. Interviewers were health staff members without special knowledge of pesticide toxicology, and who were instructed to register all answers provided by the interviewed mothers. Pesticide exposure information was further analyzed and classified according to their toxicological characteristics. Child skin color was indicated by mothers and further analyzed as white and non-white. At each center, the same interviewers were responsible for both cases and controls. Participating mothers provided written informed consent for themselves and their child.

Pesticide exposure was evaluated based on the mother's report of any contact with pesticides (at least once) during the three months before pregnancy (periconceptual period),

throughout each pregnancy trimester, or during the three months after birth (breastfeeding). They were requested to inform about any contact with pesticides at home or in the workplace during each of these pregnancy times windows of exposure. Brand names of commercial products reported by the mothers were used to determine chemical content, and associations with pesticides were explored according to: the form of use, i.e., unintentional, domestic (household), or agricultural (maternal occupational exposure, or living in an agricultural area with pesticides use); and duration and regularity of contact (no use, ≤ once a week, > once a week).

Exposures to products that included pesticides from multiple chemical classes (for instance, pyrethroids, organophosphates and carbamates), or maternal exposure to both insecticides and herbicides were also assessed, and categorized as mixed exposures whenever reported.

Ethical Aspects

This investigation was approved by the Research Ethics Committee of the Brazilian National Cancer Institute (number No. 005/06) and by the Research Ethics Committee of the Oswaldo Cruz Foundation (FIOCRUZ), No. 32/10. Participating mothers provided written informed consent for themselves and their child.

Statistical Analysis

Unconditional logistic regression was performed to estimate associations between pesticide exposures and early leukemias based odds ratios and their 95% confidence intervals after adjustment for birth weight (< 4,000 g, ≥ 4,000 g), maternal age at birth (< 35 years, ≥ 35 years), maternal schooling (≤ 8 years, > 8 years), oral contraceptive intake during pregnancy (no use, use during pregnancy), and child's skin color (white or non-white).

Sensitivity analysis was performed using different control subsets, specifically: a) after excluding controls with gastro-intestinal infections, parasitic diseases, dehydration, malnutrition or diarrhea; b) controls with respiratory illnesses, including tuberculosis, pneumonia, asthma, bronchitis, and bronchiolitis. Considering that both subsets are more prevalent among low income strata, such procedure aimed to evaluate possible confounding resulting from these controls inclusion. In addition, we estimated stratum-specific ORs according to child's skin color.

RESULTS

Origin of participants is presented at Supplemental Material, Table S1, showing a higher inclusion of children from Sao Paulo and Rio de Janeiro. Socio-demographic characteristics differed between cases and controls. Specifically, cases were more likely than controls to be white, to have mothers who were older at child's birth, more likely to have ≥8 years of education, and to have higher family income (Table 1). Complete information on model covariates was available for 85% of cases and 90% of controls. Agricultural pesticide exposures were reported by 22 (3.3%) mothers, including 7 (1.0%) who were agricultural workers.

Pesticide use at any time during the pregnancy was reported by 60.7% of AML, 36.4% of ALL, and 21.3% of control mothers of children at 0–11 months of age (Table 2). Adjusted odds ratios were 2.10 (95% CI: 1.14, 3.86) for ALL and 5.01 (95% CI: 1.97, 12.7) for AML.

For children diagnosed or enrolled at 12–23 months of age, 48.4%, 47.6% and 31.4% of AML, ALL, and controls were exposed to pesticides during pregnancy, respectively. Adjusted odds ratios were 1.88 (95% CI: 1.05, 5.23) for ALL and 1.98 (95% CI: 0.83, 4.74) for AML.

Among children diagnosed or enrolled at 0–11 months of age, information on periconceptual pesticide exposure was available for 99% of controls, 92% of ALL and 82% of AML. At age 12-23 months, they were, respectively, 95%, 63% and 71% (Table 2). ALL and AML were significantly associated with periconceptual exposures among children 0-11 months of age (adj. OR 2.40; 95% CI: 1.20, 4.81 and adj. OR 3.81; 95% CI: 1.34, 10.8, respectively). AML was significantly associated with periconceptual exposure in children age 12–23 months (adj. OR 2.48; 95% CI: 1.20, 5.11).

The odds of AML were increased with exposure during all time periods among children 0-11 months, with significant associations for pesticide exposure in the third trimester (adj. OR 3.70; 95% CI: 1.32, 10.4) and during breastfeeding (adj. OR 7.04; 95% CI: 2.47, 20.1). At age 12–23 months, they were, respectively, adj. OR 0.97; 95% CI: 0.35, 2.69 and adj. OR 1.20; 95% CI: 0.43, 3.34.

Sensitivity analysis according to the variables skin color (Supplemental Material, Table S2), diarrhea, parasitic diseases, dehydration or malnutrition (N = 98, Supplemental Material, Table S3), and respiratory diseases (Supplemental Material, Table S4) seems to support the presented results on the association between pesticides exposure and leukemia among very young children (Table 2).

Adjusted ORs for any exposure to pyrethroid pesticides during pregnancy were 1.80 (95% CI: 1.11, 2.90) for ALL and 3.39 (95% CI: 1.72, 16.78) for AML (Table 3). Adjusted ORs for use of pesticide formulations that included solvents were 1.79 (95% CI: 1.10, 2.92) for ALL and 3.45 (95% CI: 1.76, 6.74) for AML (Table 3).

The reported use of pesticide brands containing organophosphates was uncommon (1.7% of controls, 2.6% of AML and 6.8% of ALL mothers). The magnitude of association between such products and AML in very young children was adj. OR 5.50 (95% CI: 1.44, 21.03), (Table 3).

Adjusted ORs for pesticide exposure at home were 3.12 (95% CI: 1.61, 6.05) for AML, and 1.88 (95% CI: 1.20, 2.95) for ALL (Table 3). ORs for agricultural pesticide exposures were indeed higher, adj. OR 5.25; 95% CI: 1.83, 15.08 for ALL, and OR 7.56; 95% CI: 1.83, 31.23 for AML.

Compared with no reported pesticide exposure, an adjusted OR 2.88 (95% CI: 1.35, 6.17) for AML was estimated for the offspring of women reporting exposure ≤ once a week, and OR 2.94 (95% CI: 1.17, 7.38) for exposure > once a week (Table 3). For ALL, corresponding ORs were 2.19 (95% CI: 1.29, 3.69) and 2.06 (95% CI: 1.10, 3.86). Adjusted ORs for exposure to commercial products that included multiple pesticides were 5.22 (95% CI: 1.44, 19.0) for ALL, and 6.51 (95% CI: 1.25, 34.0) for AML.

A comprehensive analysis of all individual chemical components included in the reported brands revealed statistically significant associations between leukemia in very young children and maternal exposure to seven pyrethroids and unspecified solvents (Table 4). Estimates of associations with exposure to individual pyrethroids during pregnancy were imprecise due to small numbers of reported exposures. Permethrin, imiprothrin and esbiothrin exposures during pregnancy were positively associated either with ALL (adj. OR 2.47; 95% CI: 1.17, 5.25; adj. OR 2.61; 95% CI: 1.06, 6.93; adj. OR 3.03; 95% CI: 1.13, 8.09, respectively) or AML (adj. OR 7.28; 95% CI: 2.60, 20.38; adj. OR 3.41; 95% CI: 0.98, 11.90; adj. OR 3.19 95% CI: 0.77, 13.19) at age 0-11 months.

Among children age 11-23 months, esbiothrin exposures during pregnancy were positively associated with AML (adj. OR 3.71; 95% CI: 1.18, 11.62), (Table 4). Maternal exposure to Tetramethrin and D-allethrin was positively associated with AML in children 0-11 months (adj. OR 6.19; 95% CI: 2.07, 18.56 for both), while D-phenothrin was positively associated with AML in children 11-23 months of age (adj. OR 8.43; 95% CI: 1.59, 44.75), (Table 4).

DISCUSSION

Pesticides are complex mixtures that include components such as solvents, humidifying agents, emulsifiers and additives, in addition to active ingredients (Bolognesi 2003; Feron et al. 1998). Furthermore, the seasonal use of distinct formulas for specific purposes makes it difficult to present a qualitative evaluation of exposure to individual substances.

Our findings suggest that children whose mothers were exposed to pesticides 3 months before conception were at least twice as likely to be diagnosed with ALL in the first year of life compared to those who did not report such exposure. Adjusted ORs for AML in the first year of life ranged from 2.75 (95% CI: 0.96, 7.92) for any pesticide exposure in the first trimester of pregnancy, to 7.04 (95% CI: 2.47, 20.10) for exposure during breastfeeding.

Studies conducted in other countries have also reported positive associations between pesticide exposure and hematopoietic neoplasms in children, especially leukemias and lymphomas (Ma et al. 2002; Meinert at al. 2000; Menegaux et al. 2006; Rudant et al. 2007; Zahm and Ward 1998). A systematic review and meta-analysis of 15 studies of the association between residential exposure to pesticides during selected time windows (preconception, pregnancy and childhood) and childhood leukemia carried out between 1950-2009 (Turner et al. 2010), reported associations with pregnancy exposure to unspecified pesticides (OR 1.54; 95% CI: 1.13, 2.11), insecticides (OR 2.05; 95% CI: 1.80, 2.32) and herbicides (OR 1.61; 95% CI: 1.20, 2.16). Another meta-analysis of 31 studies of parental occupational exposure to pesticides and childhood leukemia (Wigle et al. 2009) reported associations with occupational exposure to insecticides (OR 2.72; 95% CI: 1.47, 5.04) and herbicides (OR 3.62; 95% CI: 1.28, 10.3) during pregnancy.

A French study also examined the association between pesticide exposure and infant leukemia (Rudant et al. 2007). According to use of any pesticide, the observed risk estimates were OR 2.3; 95% CI: 1.9, 2.8 for ALL, and OR 2.2; 95% CI: 1.4, 3.3 for AML. These authors also suggested that a domestic use of pesticides may play a role in the etiology of leukemia, and that prenatal exposure may be a window of fetal vulnerability.

Pesticide exposure during childhood may occur in many ways, either through contamination of their parents' work clothes or through household residues in water, air, soil and food (Araújo et al. 2000; Rudant et al. 2000). However, the short latency period for leukemias diagnosed during the first year of life suggests that intrauterine exposures may play a paramount role in this process.

In the Agricultural Health Study, a large prospective cohort study of approximately 49,000 pesticides applicators in the USA, an association between permethrin exposure and multiple myeloma was observed (Rusiecki et al. 2009). Compared to applicators who reported never using permethrin, the risk ratio for multiple myeloma among applicators in the highest tertile of lifetime exposure was RR 5.72 (95% CI: 2.76, 11.87). Another study of this cohort (Flower et al. 2003) reported a positive association between having a parent who applied pesticides and lymphomas diagnosed among children, age standardized incidence ratio, SIR 2.18; 95% CI: 1.13, 4.19, but not leukemias in children, SIR 0.91; 95% CI: 0.47, 1.95.

Moreover, the US Environmental Protection Agency (EPA) and the Canadian Pest Management Regulatory Agency (PMRA) have referred the occurrence of carcinogenicity following permethrin exposure in animal toxicity studies (Weichental et al. 2010). An insecticide containing imiprothrin and deltamethrin that is widely used in Egypt has been evaluated for immunotoxic effects in rats (Emara et al. 2007). The authors observed that animals exposed to both chemicals, compared to unexposed obnes, had altered levels of

splenic CD4+CD8- and CD4+CD8+ cells, and concluded that a repeated noncontinous inhalation of imiothropin and deltamethrin causes several immunotoxic effects in other distal sites to the lungs. Other pyrethroids, such as allethrin, cyhalothrin, cypermethrin, deltamethrin and tetramethrin, have also been suggested to be involved in canine mammary carcinogenesis (Andrade et al. 2010).

This research has some limitations. The hospital-based case-control study design may introduce selection bias depending on the chosen comparison groups. We recruited controls with a variety of indications for hospitalization and enrolled controls from general hospitals in the same cities, though not necessarily the same hospitals, in which the cases were diagnosed. On the other hand, the similar origin of cases and controls could theoretically induce the introduction of overmatching in relation to agriculture pesticides exposure. The reports on pesticides exposure in the agricultural set (15 ALL, 4 AML and 7 controls, Table 3) accounted for 3.3% of all participants. Therefore, we think that the occurrence of overmatching on agricultural pesticide exposure distorting the presented conclusions of this investigation is improbable.

Pesticide exposures during the examined time windows were highly correlated, with statistically significant high Pearson´s correlation coefficients, $r > 0.77$. Hence, associations with exposures during specific time of windows could not be accurately determined. Additionally, length of exposure was not evaluated in this study, so that associations according to maternal cumulative exposure to pesticides could not be estimated. Finally, sample size was limited, mainly to AML, thus resulting in imprecise estimates of association.

On the other hand, the study has some strengths, being relatively large given that the outcomes are rare. In addition, most previous studies have been based on populations from a limited number of countries, thus our study contributes for exploring the role of pesticides exposure during pregnancy and leukemias in children <2 years of age. Moreover, information

on the type of pesticide exposure, time periods of exposure, exposures to individual chemicals (mainly pyrethroids), and data on subgroups of leukemias (ALL, AML), can possibly contribute to enhance understanding of the role of maternal exposure to pesticides during pregnancy and leukemia in young children.

CONCLUSIONS

Future research will benefit from exploring the genetic and molecular mechanisms that characterize individual susceptibility to pesticide exposures in the development of leukemia in young children. However, the consistency of our findings with similar studies performed in different populations, supports recommendations for women of reproductive age to minimize their exposure to pesticides before and during pregnancy and breastfeeding.

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Table 1 - Distribution of selected socio-demographic variables, leukemia cases and controls, children < 2 yr., Brazil, 1999-2007

Characteristics	Cases (n=252) N (%)	Controls (n=423) N (%)	p-value
Sex			
Male	130 (51.6)	226 (53.4)	0.643
Female	122 (48.4)	197 (46.6)	
Missing	0	0	
Birth weight			
<4000g	234 (92.9)	393 (93.0)	0.470
≥ 4000g	16 (6.3)	21 (5.0)	
Missing	2 (0.8)	9 (2.0)	
Child's skin color			
White	170 (67.5)	153 (36.2)	< 0.001
Non-white	77 (30.5)	256 (60.5)	
Missing	5 (2.0)	14 (3.3)	
Place of Birth			
Northeast	52 (20.6)	101 (24.1)	0.552
Midwest	18 (7.1)	31 (7.3)	
Southeast	155 (61.5)	237 (56.0)	
South	27 (10.7)	54 (12.6)	
Missing	0	0	
Maternal Age (yr.) [a]			
<18	8 (3.2)	60 (14.1)	< 0.001
18-24	91 (36.1)	182 (42.9)	
25-34	117 (46.4)	145 (34.2)	
>35	36 (14.3)	36 (8.8)	
Missing	0	0	
Maternal Education (yr.)			
<8	81 (32.1)	206 (48.6)	< 0.001
≥8	146 (57.9)	209 (49.4)	
Missing	25 (10.0)	8 (2.0)	
Family Income [b]			
≤350	74 (29.4)	148 (35.0)	< 0.001
351-1750	102 (40.5)	218 (51.5)	
1751-3500	27 (10.7)	11 (2.6)	
≥3500	12 (5.0)	3 (0.7)	
Missing	37 (14.4)	43 (10.2)	
Oral Contraceptive Use			
No	223 (88.5)	404 (95.5)	< 0.001
Yes	29 (11.5)	19 (4.5)	
Missing	0	0	

Abbreviations: a-maternal age at birth; b- income in Brazilian currency, Real (R$)

Table 2 – Maternal exposure to pesticides by time window of exposure, leukemia cases and controls, children < 2 yr., Brazil, 1999-2007

Pesticide Exposure	Controls (n=423), n (%)	ALL (n=193), n (%)	AML (n=59), n (%)	ALL		AML	
				Crude OR (95% CI)	Adj OR[a] (95% CI)	Crude OR (95% CI)	Adj OR[a] (95% CI)
Pesticide use							
0-11 months							
No	200 (78.7)	56 (63.6)	11 (39.3)	1.00	1.00	1.00	1.00
Yes	54 (21.3)	32 (36.4)	17 (60.7)	2.12 (1.25-3.59)	2.10 (1.14-3.86)	5.72 (2.53-12.94)	5.01 (1.97-12.75)
Missing	0	0	0				
12-23 months							
No	116 (68.6)	55 (52.4)	16 (51.6)	1.00	1.00	1.00	1.00
Yes	53 (31.4)	50 (47.6)	15 (48.4)	1.99 (1.20-3.29)	1.88 (1.05-5.23)	2.05 (0.95-4.46)	1.98 (0.83-4.74)
Missing	0	0	0				
Periconceptual [b]							
0-11 months							
No	220 (86.6)	63 (71.6)	15 (53.6)	1.00	1.00	1.00	1.00
Yes	32 (12.6)	18 (20.4)	8 (28.6)	1.96 (1.03-3.73)	2.40 (1.20-4.81)	3.67 (1.44-9.34)	3.81 (1.34-10.84)
Missing	2 (0.8)	7 (8.0)	5 (17.8)				
12-23 months							
No	125 (74.0)	64 (61.0)	15 (48.4)	1.00	1.00	1.00	1.00
Yes	36 (21.3)	32 (30.5)	7 (22.6)	1.62 (0.61-4.28)	1.34 (0.47-3.85)	1.94 (1.04-3.61)	2.48 (1.20-5.11)
Missing	8 (4.7)	9 (8.5)	9 (29.0)				

Table 2 (continued)

Pesticide Exposure	Controls (n=423), n (%)	ALL (n=193), n (%)	AML (n=59), n (%)	ALL		AML	
				Crude OR (95% CI)	Adj OR[a] (95% CI)	Crude OR (95% CI)	Adj OR[a] (95% CI)
1st Trimester							
0-11 months							
No	219 (86.2)	63 (71.6)	16 (57.2)	1.00	1.00	1.00	1.00
Yes	32 (12.6)	18 (20.4)	7 (25.0)	1.96 (1.03-3.72)	1.86 (0.94-3.72)	2.99 (1.14-7.84)	2.75 (0.96-7.92)
Missing	3 (1.2)	7 (8.0)	5 (17.8)				
12-23 months							
No	127 (75.1)	65 (61.9)	20 (64.5)	1.00	1.00	1.00	1.00
Yes	35 (25.0)	31 (29.5)	8 (25.8)	1.73 (0.98-3.05)	1.87 (0.99-3.56)	1.45 (0.59-3.57)	1.28 (0.47-3.53)
Missing	7 (4.1)	9 (8.5)	3 (9.7)				
2nd Trimester							
0-11 months							
No	219 (86.2)	64 (72.7)	16 (57.2)	1.00	1.00	1.00	1.00
Yes	32 (12.6)	17 (19.3)	7 (25.0)	1.70 (0.89-3.25)	1.75 (0.87-3.55)	2.80 (1.08-7.32)	2.27 (0.79-6.47)
Missing	3 (1.2)	7 (8.0)	5 (17.8)				
12-23 months							
No	129 (76.2)	68 (64.8)	20 (64.5)	1.00	1.00	1.00	1.00
Yes	33 (19.5)	28 (26.7)	8 (25.8)	1.61 (0.90-2.88)	1.76 (0.91-3.39)	1.56 (0.63-3.86)	1.48 (0.54-4.04)
Missing	7 (4.1)	9 (8.5)	3 (9.7)				
3rd Trimester							
0-11 months							
No	218 (85.8)	65 (73.8)	15 (53.6)	1.00	1.00	1.00	1.00
Yes	33 (13.0)	16 (18.2)	8 (28.6)	1.63 (0.84-3.14)	1.88 (0.93-3.79)	3.52 (1.39-8.96)	3.70 (1.32-10.38)
Missing	3 (1.2)	7 (8.0)	5 (17.8)				

Table 2 (continued)

Pesticide Exposure	Controls (n=423), n (%)	ALL (n=193), n (%)	AML (n=59), n (%)	ALL		AML	
				Crude OR (95% CI)	Adj OR[a] (95% CI)	Crude OR (95% CI)	Adj OR[a] (95% CI)
3rd Trimester							
12-23 months							
No	123 (72.8)	68 (64.8)	20 (64.5)	1.00	1.00	1.00	1.00
Yes	39 (23.1)	28 (26.7)	8 (25.8)	1.30 (0.74-2.29)	1.26 (0.66-2.40)	1.26 (0.52-3.09)	0.97 (0.35-2.69)
Missing	7 (4.1)	9 (8.5)	3 (9.7)				
Breastfeeding[c]							
0-11 months							
No	229 (90.2)	69 (78.4)	14 (50.0)	1.00	1.00	1.00	1.00
Yes	22 (8.6)	12 (13.6)	9 (32.2)	1.81 (0.85-3.84)	2.05 (0.92-4.58)	6.69 (2.60-17.21)	7.04 (2.47-20.10)
Missing	3 (1.2)	7 (8.0)	5 (17.8)				
12-23 months							
No	128 (75.7)	68 (64.8)	21 (67.7)	1.00	1.00	1.00	1.00
Yes	33 (19.6)	28 (26.7)	7 (22.6)	1.60 (0.89-2.86)	1.53 (0.80-2.95)	1.29 (0.51-3.30)	1.20 (0.43-3.34)
Missing	8 (4.7)	9 (8.5)	3 (9.7)				

Abbreviations:
[a] adjusted odds ratio (adj. OR) by use of oral contraceptives during pregnancy, maternal age and education, infant birth weight and child's skin color;
[b] 3 months before pregnancy;
[c] 3 months after delivery

Table 3 - Maternal use of pesticides according to chemical class, frequency and type of use along pregnancy, leukemia cases and controls, children < 2 yr., Brazil, 1999-2007

Use of pesticides along pregnancy	Controls (N=423) N (%)	ALL (N=193), n (%)	AML (N=59), n (%)	ALL vs controls Crude OR (95% CI)	ALL vs Controls adj OR (95% C.I.) [a]	AML vs controls Crude OR (95% cI)	AML vs Controls adj OR[a] (95% CI)
Chemical Groups							
No use	316 (74.7)	111 (57.5)	27 (45.7)	1.00	1.00	1.00	1.00
Pyrethroid	89 (21.0)	63 (32.6)	25 (42.4)	2.02 (1.34-3.02)	1.80 (1.11-2.90)	3.29 (1.73-6.20)	3.39 (1.72-16.78)
Organophosphates	7 (1.7)	5 (2.6)	4 (6.8)	2.03 (0.63-6.54)	1.06 (0.26-4.32)	6.69 (1.84-24.29)	5.50 (1.44-21.03)
Other Pesticides[b]	17 (2.6)	14 (7.3)	3 (5.1)	2.66 (1.30-5.43)	2.96 (1.28-6.84)	2.66 (0.84-8.44)	1.77 (0.35-8.80)
Type of use							
No use	316 (74.7)	111 (57.5)	27 (48.2)	1.00	1.00	1.00	1.00
Household	89 (21.0)	62 (32.1)	25 (44.6)	1.98 (1.34-2.93)	1.88 (1.20-2.95)	3.29 (1.82-5.95)	3.12 (1.61-6.05)
Agriculture	7 (1.7)	15 (7.8)	4 (7.1)	6.10 (2.42-15.35)	5.25 (1.83-15.08)	6.69 (1.84-24.29)	7.56 (1.83-31.23)
Frequency							
None	315 (79.3)	111 (64.9)	27 (55.1)	1.00	1.00	1.00	1.00
Up to once/week	45 (11.3)	35 (20.5)	13 (26.5)	2.23 (1.38-3.59)	2.19 (1.29-3.69)	3.20 (1.58-6.48)	2.88 (1.35-6.17)
> once/week	37 (8.7)	25 (13.0)	9 (15.3)	1.82 (1.02-3.25)	2.06 (1.10-3.86)	2.58 (1.09-6.09)	2.94 (1.17-7.38)
Brands with mixed chemicals [c]							
No	414 (97.9)	183 (94.8)	55 (93.2)	1.00	1.00	1.00	1.00
Yes	9 (2.1)	10 (5.2)	4 (6.8)	2.51 (1.01-6.29)	5.22 (1.44-18.97)	3.35 (0.73-12.35)	6.51 (1.25-33.99)
Distinct pest classes							
No	420 (99.3)	186 (96.4)	58 (98.3)	1.00	1.00	1.00	1.00
Yes	3 (0.7)	7 (3.6)	1 (1.7)	5.27 (1.35-20.6)	18.34 (2.01-167.38)	3.35 (1.00-11.23)	8.03 (0.37-174.68)

a- Adjusted odds ratio (adj. OR) by use of oral contraceptives during pregnancy, maternal age, maternal education, birth weight and child's skin color b- Organochlorines, cumarines and others.

c- Exposure to more than one chemical in the same product or distinct products.

Table 4 – Maternal exposure to specific pesticides chemical components along pregnancy, leukemia cases and controls, children < 2 yr., Brazil, 1999-2007

Chemical compounds	Controls (N=423) n (%)	ALL (N=193) n (%)	AML (N=59) n (%)	ALL		AML	
				Crude OR (95% CI)	Adj OR[a] (95% C.I.)	Crude OR (95% CI)	Adj OR[a] (95% CI)
Prallethrin							
0-11 months							
No	234 (55.3)	78 (40.4)	23 (43.4)	1.00	1.00	1.00	1.00
Yes	3 (0.7)	1 (0.5)	2 (3.8)	1.00 (0.10-9.75)	1.52 (0.15-15.32)	6.78 (1.08-42.70)	8.06 (1.17-55.65)
12-23 months							
No	155 (36.6)	94 (48.7)	29 (54.7)	1.00	1.00	1.00	1.00
Yes	3 (0.7)	3 (1.5)	0 (0.0)	1.65 (0.33-8.34)	1.16 (0.15-9.12)	-	-
Permethrin							
0-11 months							
No	211 (49.9)	63 (32.6)	15 (28.3)	1.00	1.00	1.00	1.00
Yes	26 (6.1)	16 (8.3)	10 (18.9)	2.06 (1.04-4.08)	2.47 (1.17-5.25)	5.41 (2.20-13.28)	7.28 (2.60-20.38)
12-23 months							
No	128 (30.3)	75 (38.8)	23 (43.4)	1.00	1.00	1.00	1.00
Yes	30 (7.1)	22 (11.4)	6 (11.3)	1.25 (0.67-2.33)	1.47 (0.71-3.08)	1.11 (0.42-2.97)	1.32 (0.43-4.02)
Imiprothrin							
0-11 months							
No	223 (52.7)	67 (34.7)	20 (37.7)	1.00	1.00	1.00	1.00
Yes	14 (3.3)	12 (6.2)	5 (9.4)	2.85 (1.26-6.46)	2.61 (1.06-6.93)	3.98 (1.30-12.91)	3.41 (0.98-11.90)
12-23 months							
No	140 (33.1)	81 (42.0)	22 (41.5)	1.00	1.00	1.00	1.00
Yes	18 (4.3)	16 (8.3)	7 (13.2)	1.54 (0.74-3.18)	1.38 (0.59-3.23)	2.48 (0.93-6.61)	2.85 (0.94-8.62)

Table 4 (continued)

Chemical compounds	Controls (N=423) n (%)	ALL (N=193) n (%)	AML (N=59) n (%)	ALL		AML	
				Crude OR (95% CI)	Adj OR[a] (95% C.I.)	Crude OR (95% CI)	Adj OR[a] (95% CI)
Esbiothrin							
0-11 months							
No	227 (53.7)	68 (35.2)	21 (39.6)	1.00	1.00	1.00	1.00
Yes	10 (2.4)	11 (5.7)	4 (7.5)	3.67 (1.50-9.02)	3.03 (1.13-8.09)	4.32 (1.25-14.98)	3.19 (0.77-13.19)
12-23 months							
No	144 (34.0)	83 (43.0)	22 (41.5)	1.00	1.00	1.00	1.00
Yes	14 (3.3)	14 (7.3)	7 (13.2)	1.74 (0.79-3.82)	1.66 (0.67-4.13)	3.27 (1.19-9.00)	3.71 (1.18-11.62)
Tetramethrin							
0-11 months							
No	214 (50.6)	68 (35.2)	17 (32.1)	1.00	1.00	1.00	1.00
Yes	23 (5.4)	11 (5.7)	8 (15.1)	1.51 (0.70-3.25)	1.56 (0.65-3.72)	4.38 (1.70-11.25)	6.19 (2.07-18.56)
12-23 months							
No	134 (31.7)	78 (40.4)	27 (50.9)	1.00	1.00	1.00	1.00
Yes	24 (5.7)	17 (8.8)	2 (3.8)	1.22 (0.66-2.40)	1.35 (0.59-3.07)	0.41 (0.09-1.85)	0.47 (0.09-2.48)
D-Phenothrin							
0-11 months							
No	234 (55.3)	72 (37.3)	24 (45.3)	1.00	1.00	1.00	1.00
Yes	3 (0.7)	7 (3.6)	1 (1.9)	7.58 (1.91-30.08)	4.16 (0.85-20.29)	3.25 (0.33-32.48)	1.64 (0.16-19.68)
12-23 months							
No	155 (36.6)	93 (48.2)	25 (47.2)	1.00	1.00	1.00	1.00
Yes	3 (0.7)	4 (2.1)	4 (7.5)	2.22 (0.49-10.15)	0.69 (0.10-4.88)	8.27 (1.75-39.16)	8.43 (1.59-44.75)

Table 4 (continued)

Chemical compounds	Controls (N=423) n (%)	ALL (N=193) n (%)	AML (N=59) n (%)	ALL		AML	
				Crude OR (95% CI)	Adj OR[a] (95% C.I.)	Crude OR (95% CI)	Adj OR[a] (95% CI)
D-Allethrin							
0-11 months							
No	213 (50.3)	68 (35.2)	17 (32.1)	1.00	1.00	1.00	1.00
Yes	24 (5.7)	11 (5.7)	8 (15.1)	1.43 (0.67-3.08)	1.56 (0.65-3.72)	4.18 (1.63-10.70)	6.19 (2.07-18.56)
12-23 months							
No	132 (31.2)	78 (40.4)	27 (50.9)	1.00	1.00	1.00	1.00
Yes	26 (6.1)	19 (9.8)	2 (3.8)	1.24 (0.64-2.38)	1.54 (0.70-3.39)	0.38 (0.08-1.68)	0.46 (0.09-2.40)
Table 4 continued B							
Solvents							
0-11 months							
No	205 (48.5)	59 (30.1)	13 (24.5)	1.00	1.00	1.00	1.00
Yes	32 (7.5)	20 (10.4)	12 (22.6)	2.17 (1.16-4.07)	2.17 (1.06-4.43)	5.91 (2.48-14.10)	6.70 (2.50-17.97)
12-23 months							
No	122 (28.8)	70 (36.3)	20 (37.7)	1.00	1.00	1.00	1.00
Yes	36 (8.5)	27 (14.0)	9 (17.0)	1.31 (0.73-2.33)	1.32 (0.66-2.63)	1.52 (0.64-3.64)	1.82 (0.68-4.84)

Abbreviations:
[a] adjusted odds ratio (adj. OR) by use of oral contraceptives during pregnancy, maternal age, maternal education, birth weight and child's skin color.